(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2005 (09.09.2005)

PCT

(10) International Publication Number
WO 2005/082385 A1

(51) International Patent Classification[7]: A61K 33/24, 31/28, 31/663, 31/56, 31/57

(21) International Application Number: PCT/DK2005/000140

(22) International Filing Date: 28 February 2005 (28.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PA 2004 00313	26 February 2004 (26.02.2004)	DK
60/548, 529	26 February 2004 (26.02.2004)	US

(71) Applicant *(for all designated States except US)*: **OSTEOLOGIX A/S** [DK/DK]; c/o Symbion Science Park, Fruebjergvej 3, DK-2100 Copenhagen Ø (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HANSEN, Christian** [DK/DK]; Rungsted Strandvej 19, DK-2950 Vedbæk (DK). **NILSSON, Henrik** [SE/DK]; Cort Adelersgade 4, st. th., DK-1053 København K (DK). **CHRISTGAU, Stephan** [DK/DK]; Ræveskovsvej 10A, DK-2820 Gentofte (DK). **BONE, Henry, G., III** [US/US]; 123 Moran Road, Gross Point, MI 48236 (US).

(74) Agent: **ALBIHNS A/S**; H.C. Andersens Boulevard 49, DK-1553 Copenhagen V (DK).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/082385 A1

(54) Title: STRONTIUM-CONTAINING COMPOUNDS FOR USE IN THE PREVENTION OR TREATMENT OF NECROTIC BONE CONDITIONS

(57) Abstract: A method for the treatment and/or prophylaxis of an ostenonecrotic bone disease in a mammal in need thereof, such as, e.g., idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis, the method comprising administering an effective dose of a strontium-containing compound (a) to the mammal. A method for the treatment and/or prophylaxis of an osteonecrotic bone disease, such as, e.g., idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis and femoral head necrosis, in a mammal who is to be or is treated with a therapeutic agent (b) known to or suspected of inducing apoptosis and/or necrosis of bone cells, the method comprising administering a strontium-containing compound (a) in combination with (b).

Strontium-containing compounds for use in the prevention or treatment of necrotic bone conditions

FIELD OF THE INVENTION

The present invention relates to methods for the treatment and/or prophylaxis of necrotic bone conditions and pharmaceutical compositions for use in such treatments.

BACKGROUND OF THE INVENTION

Necrotic bone conditions, such as idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis are severe debilitating conditions. These conditions can be associated with medical interventions such as high dose glucocorticoid therapy and various treatments for HIV/AIDS, or they can arise spontaneously in susceptible individuals or as a consequence of other diseases such as Cushing syndrome, Storage diseases (i.e. Gauchers disease), haemaglobinopathies (e.g. sickle cell disease), pancreatitis, dysbaric conditions or trauma (e.g. dislocation or fracture).

Osteonecrosis is characterized by distinct histopathological features apparent on radiographs or bone scans. Although diagnostic methods for its identification have improved in recent years with the introduction of new sensitive high resolution MRI and other imaging techniques, no effective therapeutic agents or medical interventions have yet been developed to prevent and/or treat this condition.

Several pathological situations can induce osteonecrotic conditions, but among the most common clinical situations are high dose glucocorticoid use and treatments with apoptosis inducing compounds, such as the high dose anti-retroviral treatments administered to HIV infected patients.

Although most skeletal sites can be affected by osteonecrosis, the condition is most commonly found in the bone of the femoral head underneath the articular surface of the hip joint. The medical intervention of choice remains orthopedic surgery, where the necrotic bone area and affected joint structures are removed and replaced with a suitable implant. In some patients with necrotic bone disease, such as juveniles or patients with severe medical conditions, it can be highly problematic to perform this type of orthopedic surgery, and thus there is an unmet medical need for new medical therapies for prophylaxis and/or treatment of necrotic bone disease.

SUMMARY OF THE INVENTION

Accordingly, the present invention relates to a method for the treatment and/or prophylaxis of an osteonecrotic bone disease in a mammal in need thereof, such as, e.g., idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis, the method comprising administering an effective dose of a strontium-containing compound (a) to the mammal.

As described above, one of the common causes of osteonecrotic bone diseases is the treatment with therapeutic agents known to or suspected of inducing apoptosis and/or necrosis of bone cells, thereby leading to an osteonecrotic bone disease. Accordingly, the present invention also relates to a method for the treatment and/or prophylaxis of an osteonecrotic bone disease, such as, e.g., idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis and femoral head necrosis, in a mammal who is to be or is treated with a therapeutic agent (b) known to or suspected of inducing apoptosis and/or necrosis of bone cells, the method comprising administering a strontium-containing compound (a) in combination with (b).

The invention also relates to pharmaceutical compositions for use in the treatment and/or prophylaxis of osteonecrotic bone conditions.

DETAILED DESCRIPTION OF THE INVENTION

Osteonecrosis is distinct from most other metabolic bone diseases, in that the pathophysiology of the disease involves a vascular element and a regulation of the skeletal metabolism, other than seen in e.g. osteoporosis. It has been reported that some osteoporosis therapies, such as, e.g., the administration of bisphosphonates, may in fact be associated with an increased risk of developing osteonecrosis (Robinson NA & Yeo JF. Ann Acad Med Singapore. 2004; 33 (4 Suppl):48-9; Greenberg, MS. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:259-60). Accordingly, it does not appear that all of the commonly used osteoporosis therapies may be useful in the treatment of osteonecrosis.

However, the present inventors have demonstrated a therapeutic efficacy of a non-radioactive strontium salt in a model of osteonecrosis, and accordingly, the administration of a non-radioactive strontium-containing compound may in fact represent a novel and important approach for the prophylaxis as well as the treatment of an osteonecrotic bone disease in a mammal in need thereof, such as, e.g., idiopathic or secondary

osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis.

Previous studies have shown that various strontium compounds modulate bone loss in osteoporosis. *In vitro* studies have demonstrated that strontium has a direct stimulatory effect on pre-osteoblastic cell division and maturation, and a direct or matrix-mediated inhibition of osteoclast activity (Reginster, JY, *Curr Pharm Des* 2002:8 (21):1907-16). In other words, *in vitro* data indicates that strontium both works as an anti-resorptive and an anabolic agent. Various salts of strontium are known from the prior art, such as, e.g., strontium lactate, strontium chloride and strontium ranelate (distrontium salt of 2-[N,N-di(carboxymethyl)amino]-3-cyano-4-carboxymethylthiophene-5-carboxylic acid) described in EP-B 0 415 850. Other known strontium salts are e.g., strontium tartrate, strontium lactate, strontium phosphate, strontium carbonate, strontium nitrate and strontium sulfate.

Bone consists of an organic matrix comprising predominantly collagen type I, and an inorganic phase comprising calcium phosphate and calcium carbonate. Bone matrix proteins are synthesized by the osteoblasts. Formation of the organic bone matrix in turn serves as a scaffold for precipitation of the inorganic calcium salts of the bone mineral matrix, and gives the bone its structural strength. Degradation of bone is almost exclusively mediated by the multinuclear osteoclasts, which secretes acids responsible for dissolving the inorganic bone matrix and enzymes responsible for degrading the proteins of the organic bone matrix.

Normally the processes of bone resorption and bone formation are tightly coupled. Thus when bone resorption is reduced e.g. by an anti-resorptive agent, such as a bisphosphonate, bone formation will also be reduced to an almost similar extent. Conversely, if bone formation is increased e.g. by an anabolic treatment such as the hormone PTH, osteoclast recruitment and activity will also be up regulated. Strontium is reported to have an ability to uncouple bone formation and resorption processes, thus resulting in a sustained net positive bone balance. This is due to the combined actions of the strontium ion to reduce bone resorption and to increase or stabilize bone formation.

According to observations by the present inventors, it may be contemplated, that the anabolic effect of strontium on bone are of particular relevance for treatment of osteonecrotic lesions, as this property enables strontium to promote in-growth of new mineralized bone into the necrotic lesions and thus leading to repair of the condition.

In addition to this beneficial effect of strontium, the present inventors have surprisingly found that the strontium ion has an anti-apoptotic effect on bone cells, which can protect the cells from conditions inducing apoptosis such as, e.g., high dose glucocorticoid treatment or systemic administration of pro-apoptotic drugs such as, e.g., some forms of anti-retroviral or anti-neoplastic treatment. As many of the necrotic bone conditions may be associated with apoptosis of osteocytes and/or osteoblasts, the administration of a compound, which has an anti-apoptotic effect, may be of therapeutic value in the treatment and/or prophylaxis of such conditions. Accordingly, for necrotic bone conditions induced by the administration of therapeutic agents as described above, the administration of strontium-containing compounds may have a dual effect in that they both prevent the apoptosis and/or necrosis of bone cells eventually leading to an osteonecrotic bone disease, and also promote in-growth of new bone in case necrotic bone lesions caused by the apoptosis/necrosis of bone cells have already occurred.

For mammals in the need of or already in treatment with a therapeutic agent known to or suspected to induce apoptosis and/or necrosis of bone cells, it may therefore be of great value to receive an effective amount of a strontium-containing compound (a) as part of the same treatment regimen as the administration of the therapeutic agent (b).

Accordingly, the present invention relates to a method for the treatment and/or prophylaxis of an osteonecrotic bone disease, such as, e.g., idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis and femoral head necrosis, in a mammal who is to be or is treated with a therapeutic agent (b) known to or suspected of inducing apoptosis and/or necrosis of bone cells, the method comprising administering an effective dose of a strontium-containing compound (a) in combination with (b).

The present inventors have found that the administration of a strontium-containing compound (a) in combination with a therapeutic agent (b) has prophylactic and/or therapeutic value in that one or more of the following beneficial effects can be obtained:

i) reduction in the incidence or severity of the osteonecrotic bone disease, wherein the incidence or severity of the osteonecrotic bone disease is reduced by at least 5%, such as, e.g., at least 10%, at least 20%, at least 30%, at least 40% or at least 50% in patients treated with (a) and (b) in combination as compared to patients treated with (b) alone in the same dose as (b) in the combination treatment, and/or

ii) reduction of frequency and/or magnitude of side-effects of (b), wherein side effects are

being defined as any clinical relevant observation pertaining to the disease or condition in the patient, such as bone-pain, joint-pain, immobility, functional impairment, weight loss or bone mineral density (BMD) decrease, and wherein the frequency and/or magnitude of the side-effects is reduced by at least 5%, such as, e.g., at least 10%, at least 20%, at least 30%, at least 40% or at least 50% in patients treated with (a) and (b) in combination as compared to patients treated with (b) alone in the same dose as (b) in the combination treatment.

As mentioned above glucocorticoid in high doses is one of the therapeutic agents (b) known to induce osteonecrotic bone diseases by bone cell apoptosis. Glucocorticoids as well as other related steroid hormones are given in high doses to modulate immune-system responses in several clinical situations, such as organ or bone marrow transplant, inflammatory and/or autoimmune diseases and some chronic persistent inflammatory states. It has been estimated that the incidence of avascular necrosis of bone among bone marrow transplant recipients exceeds 8% by 5 years (Socie G et al. *Br J Haematol.* 1994: 86(3): 624-628). Accordingly, the therapeutic agent (b) may be a glucocorticoid and/or another steroid hormone.

Examples of other therapeutic agents known to or suspected of having a role in inducing apoptosis/necrosis of bone cells, eventually leading to osteonecrotic bone diseases, are anti-retroviral compounds, such as, e.g., efavirenz (Sustiva ®), zidovudine (Retrovir®), lamivodine (Epivir®), abacavir (Ziagen®), zalcitabine (Hivid®), didanosine (Videx®), stavudine (Zerit®), tenofovir disoproxil fumarate (Viread®), emtricitabine (Emtriva®), fosamprenavir (Lexiva®), nevirapine (Viramune®), delavirdine (Rescriptor®), capravirine, enfuvirtide (Fuzeon®), saquinavir (Invirase®, Fortovase®), ritonavir (Norvir®), indinavir (Crixivan®), tipranavir, amdoxovir, elvucitabine, atazanivir (Reyataz®), nelfinavir (Viracept®), amprenavir (Agenerase®), PRO-542, TMC-114, TMC-125, BMS-56190, DPC-0830.

Other pro-apoptotic treatments associated with osteonecrosis are cytostatic and neoplastic agents used for prevention and treatment of cancer.

Some of the therapeutic agents used in the treatment of osteoporosis are also known to induce osteonecrosis. One example of such classes of therapeutic agents is the bisphosphonates.

In a specific embodiment of the invention the strontium-containing compound (a) and the

therapeutic agent (b) are administered as separate compositions. The administration of (a) and (b) may take place simultaneously or sequentially, dependent on the type of therapeutic agent (b), the treatment regimen of (b), the nature of the disease towards which (b) is administered and the impact of (b) on the bone cells of the mammal receiving (b).

In one situation the therapeutic agent (b) is known to induce apoptosis and/or necrosis of bone cells and is administered according to the normal treatment regimen of (b) for the specific disease towards which (b) is administered. In such a situation, the strontium-containing compound (a) may be administered before the administration of (b) or simultaneously with (b). In case (a) is administered before (b), the administration of (a) may e.g. take place several hours, days or weeks or more before the administration of (b).

In case of high dose glucocorticoid treatment for e.g. an autoimmune disease such as systemic lupus erythomatosus (SLE), administration of a strontium compound (a) may be started simultaneously with high dose glucocorticoid (b). In situations where glucocorticoid treatment can be anticipated in advance, such as e.g. in treatment for patients receiving a renal transplant, the strontium compound (a) may be administered in advance of the glucocorticoid (b), such as e.g. on month, two weeks or one week or more before.

In another situation, the therapeutic agent (b) is only suspected to induce apoptosis and/or necrosis of bone cells. In this situation, the administration of the strontium-containing compound may not be initiated until effects of (b) on bone cells can be demonstrated. Accordingly, in such a situation the administration of (a) may be initiated with a substantial time delay to the initiation of the administration of (b), such as, e.g. several days or weeks.

An example of this is osteonecrosis associated with antiretroviral therapy (b) in HIV, where the length of treatment duration is a significant risk factor for osteonecrosis development; treatment with a strontium compound (a) may be initiated up to 5 years or more after treatment with the antiretroviral therapy (b) is started.

Even though the strontium-containing compound (a) and the therapeutic agent (b) are administered sequentially, e.g. within a time interval of several hours, days, weeks, months or even years, they are still considered to be part of the same treatment.

The administration of the strontium-containing compound (a) may take place one or more times daily, such as, e.g., from 2-5 times daily. The administration may also take place

one or more times weekly, such as from 1 to 3 times weekly.

The strontium-containing compound (a) may be administered the same number of times per day or e.g. week as (b), or (a) may be administered less times per day or e.g. week than (b) or more times per day or e.g. week than (b), dependent on the total daily or weekly dose of (a) needed. Even though (a) and (b) are not administered the same number of times per day or e.g. week, they are still considered to be part of the same treatment.

The administration of the strontium-containing compound (a) may be by the enteral or parenteral route or by topical administration. In a specific embodiment of the invention the administration is by the oral route.

In a specific method according to the invention the strontium-containing compound (a) and the therapeutic agent (b) are administered as a single composition.
Irrespectively of the method used for treatment and/or prophylaxis of the osteonecrotic bone conditions, i.e. whether the strontium-containing compound is administered alone, or used in a combination treatment together with a therapeutic agent (b) as described above, the following applies:

The strontium-containing compound (a) may be selected from the group consisting of strontium salts of an organic or an inorganic acid, and the salts may be in hydrate, anhydrous, solvate, polymorphous, amorphous, crystalline, microcrystalline or polymeric form. In one embodiment of the invention only non-radioactive isotopes of strontium are used.

The inorganic acid for making strontium salts may be selected from the group consisting of boric acid, bromous acid, carbonic acid, chloric acid, diphosphoric acid, disulfuric acid, dithionic acid, dithionous acid, fulminic acid, hydrazoic acid, hydrobromic acid, hydrochloric acid, hydrofluoric acid, hydroiodic acid, hydrogen sulfide, hypophosphoric acid, hypophosphorous acid, iodic acid, iodous acid, metaboric acid, metaphosphoric acid, metaphosphorous acid, metasilicic acid, nitric acid, nitrous acid, orthophosphoric acid, orthophosphorous acid, orthosilicic acid, phosphoric acid, phosphinic acid, phosphonic acid, phosphorous acid, pyrophosphorous acid, selenic acid, sulfonic acid, sulfuric acid, sulfurous acid, thiocyanic acid and thiosulfuric acid.

The organic acid may be selected from the group consisting of acetic acid, C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_4(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, malonic acid, lactic acid, citric acid, tartaric acid, oxalic acid, ascorbic acid, benzoic acid, salicylic acid, pyruvic acid, L- and D-aspartic acid, phthalic acid, carbonic acid, formic acid, methanesulfonic acid, ethanesulfonic acid, camphoric acid, gluconic acid, L- and D-glutamic acid, trifluoroacetic acid, ranelic acid, 2,3,5,6-tetrabromobenzoic acid, 2,3,5,6-tetrachlorobenzoic acid, 2,3,6-tribromobenzoic acid, 2,3,6-trichlorobenzoic acid, 2,4-dichlorobenzoic acid, 2,4-dihydroxybenzoic acid, 2,6-dinitrobenzoic acid, 3,4-dimethoxybenzoic acid, abietic acid, acetoacetic acid, acetonedicarboxylic acid, aconitic acid, acrylic acid, adipic acid, alanine, alpha-ketoglutaric acid, anthranilic acid, benzilic acid, arachidic acid, arginine, aspartic acid, asparagine, azelaic acid, behenic acid, benzenesulfonic acid, beta-hydroxybutyric acid, brassidic acid, capric acid, chloroacrylic acid, cinnamic acid, citraconic acid, crotonic acid, cyclopentane-1,2-dicarboxylic acid, cyclopentanecarboxylic acid, cystathionine, ranelic acid, decanoic acid, erucic acid, ethylenediaminetetraacetic acid, fulvic acid, fumaric acid, gallic acid, glutaconic acid, glutamic acid, glutamine, glutaric acid, gulonic acid, glycine, heptanoic acid, hexanoic acid, histidine, humic acid, hydroxystearic acid, isoleucine, isophthalic acid, itaconic acid, lanthionine, lauric acid (dodecanoic acid), leucine, levulinic acid, linoleic acid (cis,cis-9,12-octadecadienoic acid), lysine, malic acid, m-chlorobenzoic acid, melissic acid, mesaconic acid, methacrylic acid, monochloroacetic acid, myristic acid, (tetradecanoic acid), nonanoic acid, norvaline, octanoic acid, oleic acid (cis-9-octadecenoic acid), ornithine, oxaloacetic acid, palmitic acid (hexadecanoic acid), p-aminobenzoic acid, p-chlorobenzoic acid, petroselic acid, phenylacetic acid, phenylalanine, p-hydroxybenzoic acid, pimelic acid, propiolic acid, propionic acid, proline, serine, p-tert-butylbenzoic acid, p-toluenesulfonic acid, threonine, tryptophan, tyrosine, pyruvic acid, sarcosine, sebacic acid, serine, sorbic acid, stearic acid (octadecanoic acid), suberic acid, succinic acid, terephthalic acid, tetrolic acid, threonine, thyronine, tricarballylic acid, trichloroacetic acid, trimellitic acid, trimesic acid, tyrosine, ulmic acid, valine and cylohexanecarboxylic acid.

All acids, which the United States Food and Drug Administration (FDA) has regarded as safe for use in compositions for oral intake, may be used in the present invention. In one embodiment of the invention the acid may be a monoprotic or a diprotic acid. In yet another embodiment of the invention, the acid may be an amino acid in either the L-form or D-form or any mixture thereof.

Specific examples of strontium salts for use according to the invention are strontium chloride, strontium chloride hexahydrate, strontium citrate, strontium malonate, strontium succinate, strontium fumarate, strontium ascorbate, strontium aspartate in either L and/or D-form, strontium glutamate in either L- and/or D-form, strontium alpha-ketoglutarate strontium pyruvate, strontium tartrate, strontium glutarate, strontium maleate, strontium methanesulfonate, strontium benzenesulfonate, strontium ranelate and mixtures thereof.

In a specific embodiment of the invention, the strontium salt is composed of a strontium ion complexed to a di-carboxylic organic acid. Such a salt may also be a salt of an amine or an amino acid or mixtures thereof. A strontium salt of a di-carboxylic acid may be selected so the di-carboxylic acid moiety of the composition has a higher dissolution constant to strontium ions compared to calcium ions under physiological conditions. Thus, the dissolved salt will provide a solution with preferential binding of free calcium ions which may provide an advantage for promoting intestinal absorption of the strontium ion and thus improving the therapeutic effect and/or reducing the required dose necessary to achieve the prophylactic and/or therapeutic effect in the osteonecrotic condition.

The daily dose of ionic strontium may be at least about 0.01 g, such as, e.g. at least about 0.025 g, at least about 0.050 g, at least about 0.075 g, at least about 0.1 g, at least about 0.2 g, at least about 0.3 g, at least about 0.4 g or at least about 0.5 g or from about 0.01 to about 2 g such as, e.g., from about 0.1 to about 2 g, from about 0.1 to about 1 g, from about 0.15 to about 0.5 g, from about 0.3 to about 2 g or from about 1 to about 2 g.

In the case that the strontium-containing compound is strontium malonate, it may be administered in a dose corresponding to from about 0.1 to about 10 g daily calculated as anhydrous salt. More specifically, the salt may be administered in a dose corresponding to from about 0.2 to about 8 g daily such as, e.g., from about 0.4 to about 5 g daily, from about 0.6 to about 3 g daily or from about 0.7 to about 2 g daily calculated as anhydrous salt.

In case another strontium salt is used, the person skilled in the art will be able to calculate the total daily doses of strontium salt dependent on the counter-ion and the desired daily dose of ionic strontium.

As mentioned above, the administration of the strontium-containing compound (a) may take place one or more times daily, such as from 2 to 5 times daily. The administration may take place one or more times weekly, such as from 1 to 3 times weekly.

The administration of (a) may be by the enteral or parenteral route or by topical administration. In a preferred embodiment, the administration is by the oral route.

The mammal to be treated in a method according to the invention may be a human or a domestic animal, such as, e.g., a cat, a dog, a horse, a cow or a sheep. In a preferred embodiment the subject to be treated is a human, such as, e.g. a human female or male adult, adolescent or child.

The mammal in need of treatment may be identified and/or monitored by imaging techniques such as, e.g., X-ray, ultrasound, magnetic resonance imaging of the skeletal site suspected to be at risk for osteonecrosis and/or by assessment of altered bone turnover by the use of specific biochemical markers of bone turnover.

The details and specifics described above applies *mutatis mutandis* to the following:

In addition to the methods described above, the invention also relates to the use of a strontium-containing compound (a) for the manufacture of a medicament for treating and/or preventing an osteonecrotic bone condition, such as, e.g. idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis, in a mammal.

The invention also relates to the use of a strontium containing-compound (a) and a therapeutic agent (b) for the manufacture of a medicament for treating and/or preventing an osteonecrotic bone condition in a mammal, wherein (b) is known to or suspected of inducing apoptosis and/or necrosis of bone cells leading to an osteonecrotic bone condition.

The invention further relates to a pharmaceutical composition comprising a strontium-containing compound (a), and a therapeutic agent (b) that is known to or suspected of inducing apoptosis and/or necrosis of bone cells leading to an osteonecrotic bone condition, optionally together with one or more pharmaceutically acceptable excipients, i.e. a therapeutically inert substance or carrier.

The carrier may take a wide variety of forms depending on the desired dosage form and administration route.

The pharmaceutically acceptable excipients may be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavors, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

Above are mentioned specific examples of the amounts of compounds administered. However, it will be understood that the amount of the compounds actually administered will be determined by a physician in light of the relevant circumstances including the condition to be treated, the choice of compounds to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the chosen route of administration. While the present compositions are preferably administered orally, the compounds may also be administered by any other suitable route.

The pharmaceutical composition according to the invention may be in the form of a solid, semi-solid or fluid composition. In one embodiment of the invention, the pharmaceutical composition may be in the form of a tablet. The tablet may be coated with a coating that enables release of at least part of the salt in the proximal part of the small intestine, such as e.g. the duodenum and/or the proximal jejunum, such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the salt contained in the tablet.

In another embodiment of the invention a compound may be selected have complete or predominant solubility in the ventricle such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the salt contained in the tablet.

The tablet may have a shape that makes it easy and convenient for a patient to swallow. The tablet may thus e.g. have a rounded or a rod-like shape without any sharp edges. Furthermore, the tablet may be designed to be divided in two or more parts.

A semi-solid form of the composition may be a paste, a gel or a hydrogel.

The fluid form of the composition may be a solution, an emulsion including nano-emulsions, a suspension, a dispersion, a liposomal composition, a spray, a mixture, a syrup or an elixir.

Other suitable dosages forms of the pharmaceutical compositions according to the invention may be capsules, sachets, troches, devices etc.

The pharmaceutical compositions may be prepared by any of the methods well known to a person skilled in pharmaceutical formulation.

The invention also relates to a kit comprising two or more components, the first component comprising a strontium-containing compound (a) and the second component comprising a therapeutic agent (b) that is known to or suspected of inducing apoptosis and/or necrosis of bone cells leading to an osteonecrotic bone condition.

In certain cases it may be beneficial to include one or more further active substances in a method, a pharmaceutical composition or a kit according to the invention. The one or more further active substances may have a therapeutic and/or prophylactic effect on an osteonecrotic bone disease, such as, e.g., osteonecrosis. The term "active substance having a therapeutic and/or prophylactic effect on an osteonecrotic bone disease" includes active substances that can attain a particular medical result, such as, e.g., reduce the incidence of osteonecrosis, reduce bone pain associated with the osteonecrotic lesion increase bone density and/or improve healing of bone or prevent the occurrence of fracture in a subject at risk of developing an osteonecrotic condition. Examples of such substances are bone anti-resorptive and/or anabolic agents. However, one or more active substances having other effects than those mentioned above may also be included in a method or a pharmaceutical composition of the invention. Such active substances could be e.g. pain relievers (analgesic agents), anti-inflammatory agents, anti-retroviral agents, anti-neoplastic agents, disease-modifying anti-rheumatic drugs, or other anti-rheumatic drugs.

Specific examples of active substances, which may be used in a method or a pharmaceutical composition according to the invention are calcium-alpha-ketoglutarate, calcium and/or salts thereof, vitamin D such as, e.g., vitamin D3 and/or functional equivalents of vitamin D3, glucagon-like peptide-2, glucagons-like peptide-2 releasing compositions, non-steroidal anti-inflammatory drugs, pain relieving agents tumor necrosis factor alpha (TNF-α) inhibitors, inhibitors of IL-15 release or function and inhibitors of IL-1 release or function.

The following examples intend to illustrate the invention without limiting it in any way.

EXAMPLES

Example 1

Effect of strontium malonate in an animal model of osteonecrosis

The rationale for the study was to assess the ability of strontium to act as a therapeutic and bone growth promoting (i.e. pro-anabolic) agent in an animal model of osteonecrosis. In this model, a syngenic necrotic bone graft was implanted into the femur of a recipient rat. The necrotic graft was degraded, while ingrowth of new bone occurred. At termination of the experiment, the structural grafts was removed and analyzed by histology to quantify both the degradation of the necrotic graft as well as ingrowth of new bone. Concomitant treatment with anabolic and/or anti-resorptive agents may be given after the insertion of the necrotic graft, and the effect monitored after termination of the experiment. This rat model has previously been described (*Åstrand J, Aspenberg P. BMC Musculoskelet Disord. 2002;3(1):19*).

Methods and Materials

The compounds (active strontium test-article: Sr-malonate, 189.6 g/mol; Placebo substance, calcium malonate, 142.1 g/mol) was suspended in drinking water for the rats. The salts were prepared in a solution of 1.6 g/l, which is close to saturation (22 – 25°C). Thus extensive stirring was required to completely dissolve the substances. A new batch of drinking water was prepared fresh every week for the duration of the experiment. When not in use the solution was stored at room temperature in a closed container. Preliminary experiments showed that the animals each drink between 60 and 90 ml/24 h resulting in approximate strontium dosing of 120 mg strontium malonate/day equal to 55.4 mg of ionic strontium.

The study was performed in 20 male Sprague-Dawley rats ca. weight 350 g (corresponding to an age of 9 – 10 weeks), Taconic M&B, Lille Skensved, Denmark. The animals were allowed 2 weeks acclimatization before initiation of the experiment and were accordingly approximately 12 weeks old at implantation of the necrotic bone graft (week 0).

The study consisted of 2 groups each of 10 rats. The rats were randomly allocated to the groups before the initiation of the study. As in previous studies with therapeutic interventions in this model of osteonecrosis (*Astrand J, Aspenberg P. BMC Musculoskelet Disord. 2002;3(1):19*) the study lasted for 6 weeks. At week 0 they were subjected to an operation with insertion of a necrotic bone graft, with cancelous (trabecular) bone grafts

derived from female Sprague Dawley rats. The bone graft were excised from the female rats after necropsy, and frozen at -80°C to kill all cells within the bone graft. The graft was then placed into a titanium chamber placed in the tibia of the right hind leg, in operation at full anesthesia. Treatment with strontium malonate or control (calcium malonate) was initiated from week 0. Food and water containing the suspended test substance was administered ad libitum. The rats were euthanized after 6 weeks, and the titanium chambers containing the necrotic bone grafts were removed and processed for histological assessment.

After careful removal from the titanium chamber, the grafts were decalcified in 10 % formic acid, 2 % formaldehyde for 14 days. The decalcified skeletal tissue was embedded in paraffin and cut in 1 µm sections parallel to the long axis of the graft. Each section was subsequently stained with hematoxylin and eosin, and visually scored for appearance of degradation of the necrotic graft as well as ingrowth of new bone.

Results

All 20 animals completed the 6 week study period, and were available for histological analysis. The histological analysis showed that in all rats, soft tissue had invaded the grafts. New bone had formed a bone ingrowth frontier. The main parameter of analysis was the measurement of this ingrowth distance. The two groups of animals showed significant differences in the extent of ingrowth of new bone. The strontium malonate treated group had an average ingrowth of 3.43 (± 1.35 (SD)) mm compared to an average ingrowth of 2.24 (± 1.00) p=0.038. This shows that strontium malonate had a significant anabolic effect, and thus indicates the potential use of this compound in both prophylaxis and treatment of osteonecrosis.

The strontium malonate used in the Examples herein has been prepared as described below:

<u>Preparation of strontium malonate anhydrate by synthesis at 100 °C</u>

Initially, a suspension of malonic acid (white colored) was prepared by adding 100 mL of millipore water to 10.406 g (0.1 moles) of solid malonic acid (Fluka, MW 104.06 g/mole, CAS no. 141-82-2, lot. no. 449503/1, filling code 44903076) in a 250 mL beaker. To this suspension was added 26.571 g (0.1 moles) of solid strontium hydroxide (Sigma Aldrich, $Sr(OH)_2*8H_2O$, MW 265.71, CAS no. 1311-10-0). Then, a magnetic stirring rod was added and the stirring and heating was started to the point of boiling of the suspension. The final suspension was also white colored and the stirring was sustained by maintaining a

medium rotation rate of the stirring apparatus. In order to prevent carbon dioxide from entering the solution, the beaker was covered by a covering glass.

After some minutes of boiling and stirring, the solution clarified and all the solid material dissolved. The boiling was maintained, and additional water was added when required, as to replace the water lost by boiling. After three hours of boiling, the solution was filtered while boiling on a Büchner funnel. Very small amounts of impurities were left in the filter. The filtrate was subsequently allowed to cool to room temperature, which resulted in growth of fine-powdered crystals of strontium malonate. Precipitation of the final product progressed rapidly during filtration and the majority of the product was found in the filter (unheated). Only in rare instants, the precipitation progressed in the filtrate. The product was filtered and dried at 110 ^{0}C in an oven for ½ hour followed by drying 12 hours in a dessicator over silica orange. Before analysis by x-ray crystallography and by Flame Atomic Absorption Spectrometry (F-AAS), the salts were ground by a mortar to fine powder.

The total yield of strontium malonate was approximately 98% before recrystallisation, and the majority of impurities consisted of reminisces of the reagents and of strontium carbonate. The product was unambiguously identified as strontium malonate (anhydrous) by x-ray crystallography and comparing the data to results of the Cambridge Crystallographic Database.

In a further improvement of the synthesis, anhydrous strontium malonate was produced in 10 kg scale in a method according to the present invention indicative of the applicability of the method for larger scale synthesis. 15.80 kg $Sr(OH)_2*8H_2O$ was dissolved in 63.2 l purified water and heated to 95 – 100°C. 5.63 kg malonic acid was dissolved in 4.1 l purified water, filtered where after an additional 1.4 l of water was added and the solution heated to 95 –100°C. The two solutions were mixed in a closed reaction vessel under an inert nitrogen atmosphere and stirred under reflux for 20 min. Subsequently the heating was stopped and the solution was allowed to cool to 40 – 50°C over 2 – 4 hours while strontium malonate was allowed to precipitate. The precipitate was filtered and the salt washed with an additional 13.2 l of water, followed by drying to complete dryness at vacuum in a temperature of 70°C. 9.4 kg anhydrous highly pure strontium malonate was obtained as a uniform microcrystalline white powder, corresponding to a yield of 94%. The product was unambiguously identified as strontium malonate (anhydrous) by x-ray crystallography and comparing the data to results of the Cambridge Crystallographic Database.

Tablet for use in a method according to the invention may be prepared as follows:

Formulation of strontium malonate in tablets.

Strontium malonate can be formulated for pharmaceutical use in convenient tablets for oral administration. The tablets should be prepared with microcrystalline strontium malonate manufactured as described above. For production of the tablets the following procedure can be followed, which will result in approximately 12000 tablets.

3600g Strontium Malonate, prepared as described above is mixed with 180 g Avicel PH102 (microcrystalline cellulose) Ph. Eur. After blending 144g Polyvidone A Ph. Eur. And 450 g Purified Water Ph. Eur. is added to the mixture.

The weight of the mixture is controlled (theoretical weight 3924 g). After completion of the mixing process, the granulate material is sieved through a net with a pore size of 1.2 mm and dried at 40°C in trays in a suitable drying oven. To the granulate is added 23 g Colloidal Anhydrous Silica (Aerosil 200) Ph. Eur, 284 g Avicel PH102 (microcrystalline cellulose) Ph. Eur. and 23 g Magnesium Stearate Ph. Eur. Thorough mixing is performed, and the material is sieved through a net with a pore size of 0.7 mm. This material is loaded on a tablet pressing machine.

Nine mm white round tablets (ø 9 mm) with no score line are manufactured, each containing the following ingredients:

Strontium malonate	300 mg
Microcrystalline Cellulose Ph.Eur.	43,5 mg
Polyvidone Ph,Eur.	12 mg
Colloidal anhydrous silica Ph.Eur.	2,25 mg
Magnesium Stearate Ph.Eur.	2,25 mg

In Pharmaceutical use for administering a 1.2 g dose of strontium malonate 4 tablets can be administered to a subject in need thereof. It follows that a person skilled in the art, by employing a tablet pressing machine with larger press heads can produce larger tablets containing more of the listed ingredients but with the same relative abundance.

CLAIMS

1. A method for the treatment and/or prophylaxis of an osteonecrotic bone disease in a mammal in need thereof, such as, e.g., idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis, the method comprising administering an effective dose of a strontium-containing compound (a) to the mammal.

2. A method according to claim 1, wherein the daily dose of strontium is at least about 0.01 g, such as, e.g. at least about 0.025 g, at least about 0.050 g, at least about 0.075 g, at least about 0.1 g, at least about 0.2 g, at least about 0.3 g, at least about 0.4 g or at least about 0.5 g or from about 0.01 to about 2 g such as, e.g., from about 0.1 to about 2 g, from about 0.1 to about 1 g, from about 0.15 to about 0.5 g, from about 0.3 to about 2 g or from about 0.5 to about 2 g.

3. A method according to claim 1 or 2, wherein the administration takes place one or more times daily.

4. A method according to claim 3, wherein the administration takes place from 2-5 times daily.

5. A method according to any of the preceding claims, wherein the administration is by the enteral or parenteral route or by topical administration.

6. A method according to claim 5, wherein the administration is by the oral route.

7. A method for the treatment and/or prophylaxis of an osteonecrotic bone disease, such as, e.g., idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis and femoral head necrosis, in a mammal who is to be or is treated with a therapeutic agent (b) known to or suspected of inducing apoptosis and/or necrosis of bone cells, the method comprising administering a strontium-containing compound (a) in combination with (b).

8. A method according to claim 7, wherein the apoptosis and/or necrosis of bone cells lead to an osteonecrotic bone disease.

9. A method according to claim 7 or 8, wherein the administration of the strontium-

containing compound (a) and the therapeutic agent (b) leads to at least one of the following:

i) reduction in the incidence or severity of the osteonecrotic bone disease, wherein the incidence or severity of the osteonecrotic bone disease is reduced by at least 5%, such as, e.g., at least 10%, at least 20%, at least 30%, at least 40% or at least 50% in patients treated with (a) and (b) in combination as compared to patients treated with (b) alone in the same dose as (b) in the combination treatment,

ii) reduction of frequency and/or magnitude of side-effects of (b), wherein side effects are being defined as any clinical relevant observation pertaining to the disease or condition in the patient, such as bone-pain, joint-pain, immobility, functional impairment, weight loss or bone mineral density (BMD) decrease, and wherein the frequency and/or magnitude of the side-effects is reduced by at least 5%, such as, e.g., at least 10%, at least 20%, at least 30%, at least 40% or at least 50% in patients treated with (a) and (b) in combination as compared to patients treated with (b) alone in the same dose as (b) in the combination treatment.

10. A method according to any of claims 7-9, wherein the therapeutic agent (b) is a glucocorticoid and/or another steroid hormone.

11. A method according to any of claims 7-9, wherein the therapeutic agent (b) is an anti-retroviral compound, such as, e.g., efavirenz (Sustiva ®), zidovudine (Retrovir®), lamivodine (Epivir®), abacavir (Ziagen®), zalcitabine (Hivid®), didanosine (Videx®), stavudine (Zerit®), tenofovir disoproxil fumarate (Viread®), emtricitabine (Emtriva®), fosamprenavir (Lexiva®), nevirapine (Viramune®), delavirdine (Rescriptor®), capravirine, enfuvirtide (Fuzeon®), saquinavir (Invirase®, Fortovase®), ritonavir (Norvir®), indinavir (Crixivan®), tipranavir, amdoxovir, elvucitabine, atazanivir (Reyataz®), nelfinavir (Viracept®), amprenavir (Agenerase®), PRO-542, TMC-114, TMC-125, BMS-56190, DPC-0830, .

12. A method according to any of claims 7-9, wherein the therapeutic agent (b) is a bisphosphonate.

13. A method according to any of claims 7-12, wherein the daily dose of strontium is at least about 0.01 g, such as, e.g. at least about 0.025 g, at least about 0.050 g, at least about 0.075 g, at least about 0.1 g, at least about 0.2 g, at least about 0.3 g, at least about

0.4 g or at least about 0.5 g or from about 0.01 to about 2 g such as, e.g., from about 0.1 to about 2 g, from about 0.1 to about 1 g, from about 0.15 to about 0.5 g, from about 0.3 to about 2 g or from about 1 to about 2 g.

14. A method according to any of claims 7-13, wherein (a) and (b) are administered as a single composition.

15. A method according to any of claims 7-13, wherein (a) and (b) are administered as separate compositions.

16. A method according to any of claims 7-15, wherein the administration of (a) and (b) take place simultaneously or sequentially.

17. A method according to any of claims 1 to 16, wherein the strontium-containing compound (a) is selected from the group consisting of strontium salts of an organic or an inorganic acid.

18. A method according to claim 17, wherein the salt is in hydrate, anhydrous, solvate, polymorphous, amorphous, crystalline, microcrystalline or polymeric form.

19. A method according to any of claims 1-18, wherein the salt is selected from the group comprising strontium chloride, strontium carbonate, strontium citrate, strontium malonate, strontium succinate, strontium fumarate, strontium ascorbate, strontium pyruvate, strontium L-glutamate, strontium D-glutamate, strontium L-aspartate, strontium D-aspartate, strontium alpha-ketoglutarate, strontium lactate, strontium tartrate, strontium glutarate, strontium maleate, strontium methanesulfonate, strontium benzenesulfonate, strontium ranelate and mixtures thereof.

20. Use of a strontium-containing compound (a) for the manufacture of a medicament for treating and/or preventing an osteonecrotic bone condition, such as, e.g. idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis, in a mammal.

21. Use of a strontium containing-compound (a) and a therapeutic agent (b) for the manufacture of a medicament for treating and/or preventing an osteonecrotic bone condition in a mammal, wherein (b) is known to or suspected of inducing apoptosis and/or

necrosis of bone cells leading to an osteonecrotic bone condition.

22. A pharmaceutical composition comprising a strontium-containing compound (a), and a therapeutic agent (b) that is known to or suspected of inducing apoptosis and/or necrosis of bone cells leading to an osteonecrotic bone condition, optionally together with one or more pharmaceutically acceptable excipients.

23. A kit comprising two or more components, the first component comprising a strontium-containing compound (a) and the second component comprising a therapeutic agent (b) that is known to or suspected of inducing apoptosis and/or necrosis of bone cells leading to an osteonecrotic bone condition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2005/000140

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K33/24 A61K31/28 A61K31/663 A61K31/56 A61K31/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 03/028742 A (COCKBAIN JULIAN ; FAGERLUND BJOERN JARL (NO); JELLUM EGIL (NO); SANTOS) 10 April 2003 (2003-04-10) pages 3-11; claims 16,17; examples 14-16,19,33	22,23 5-7,10, 15-19
X	EP 0 737 471 A (L'OREAL) 16 October 1996 (1996-10-16) page 4, lines 2-5; claims 8-13,19,34,38,43; example 20	22,23
A	BROUSSE C: "Osteoarticular complications of corticotherapy" HEPATO-GASTRO 2000 FRANCE, vol. 7, no. 3, 2000, pages 173-178, XP008040683 ISSN: 1253-7020 page 176, left-hand column, paragraphs 2,3	1,7,9, 10,15, 16,22

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2005	26/07/2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Kanbier, D

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/DK2005/000140

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"DEPISTAGE ISOTOPIQUE DE L'OSTEONECROSE" NOUVELLE PRESSE MEDICALE, PRESSE MEDICALE, PARIS, FR, vol. 2, no. 9, 3 March 1973 (1973-03-03), page 583, XP008040684 ISSN: 0301-1518 the whole document	1-21
A	BEERS, BERKOW (EDS): "The Merck Manual of diagnosis and therapy, 17th edn" 1999, MERCK RESEARCH LABORATORIES , XP002334211 pages 453-454	1-21
A	SOERDJBALIE-MAIKOE, VIDYA ET AL: "Strontium-89 (Metastron) and the bisphosphonate olpadronate reduce the incidence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton" EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING , 29(4), 494-498 CODEN: EJNMA6, 2002, XP008040694 page 497 page 495	1,9,12, 15-19, 21,22
A	MARIE, P. J. ET AL: "Mechanisms of action and therapeutic potential of strontium in bone" CALCIFIED TISSUE INTERNATIONAL , 69(3), 121-129 CODEN: CTINDZ; ISSN: 0171-967X, 2001, XP008040696 pages 121-125 page 127, right-hand column	1,9,14, 16-20
A	REGINSTER J-Y: "Strontium ranelate in osteoporosis" CURRENT PHARMACEUTICAL DESIGN 2002 NETHERLANDS, vol. 8, no. 21, 2002, pages 1907-1916, XP008024667 ISSN: 1381-6128 page 1908, left-hand column, paragraph 2 page 1909, right-hand column, paragraph 4 page 1915	1,9,14, 16-19, 21,22

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2005/000140

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MARIE P J ET AL: "AN UNCOUPLING AGENT CONTAINING STRONTIUM PREVENTS BONE LOSS BY DEPRESSING BONE RESORPTION AND MAINTAING BONE FORMATION IN ESTROGEN-DEFICIENT RATS" JOURNAL OF BONE AND MINERAL RESEARCH, NEW YORK, NY, US, vol. 8, no. 5, 1 May 1993 (1993-05-01), pages 607-615, XP000646111 ISSN: 0884-0431 page 608, left-hand column	1,9,14, 16-19,22
A	US 2002/018748 A1 (SATZ ROSEANNE ET AL) 14 February 2002 (2002-02-14) paragraphs '0005!, '0007!; claim 1	1,9,14, 16-19,22

INTERNATIONAL SEARCH REPORT

national application No.
PCT/DK2005/000140

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]ional Application No
PCT/DK2005/000140

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03028742 A	10-04-2003	CA	2499814 A1	10-04-2003
		CN	1585646 A	23-02-2005
		EP	1429792 A1	23-06-2004
		WO	03028742 A1	10-04-2003
		JP	2005507396 T	17-03-2005
		US	2005013877 A1	20-01-2005
EP 0737471 A	16-10-1996	FR	2732599 A1	11-10-1996
		FR	2732600 A1	11-10-1996
		FR	2732601 A1	11-10-1996
		FR	2732602 A1	11-10-1996
		CA	2173689 A1	11-10-1996
		EP	0737471 A2	16-10-1996
		NO	961371 A	11-10-1996
		US	5851556 A	22-12-1998
		FR	2732603 A1	11-10-1996
US 2002018748 A1	14-02-2002	NONE		